REMARKS

Entry of this amendment and reconsideration of the rejection of the claims is respectfully requested.

Claims 1-54, 102, and 115-120 are cancelled without prejudice or disclaimer. These claims were subject to a restriction requirement. Claim 56 is also cancelled. Applicants reserve the right to pursue the cancelled subject matter in one or more continuing or divisional applications.

Claims 55, 57-59, 66-72, 75, 84, 88-89, 93-95, 105-109 and 113 are newly amended herein. Support for the amendments to claims 55, 66 and 105 is found, for example, in original claim 1; and, elsewhere throughout the specification.

Claims 57-59, 66-72, 75, 84, 88-89, and 106-109 are amended to more clearly claim the invention and to correct grammatical errors. Support for the amendments to claims 57, 58, 69-72, 75, 88-89, and 106-109, is found, for example, within the individual claim and elsewhere throughout the specification.

Claims 93-95 are amended to remove the language "of interest". Claim 113 is amended to correct antecedent basis and grammatical error. Support the amendments to the claim is found, for example, in original 113 as filed, and, elsewhere throughout the specification. No new matter is believed to be added by way of this amendment and entry is respectfully requested.

Claim 86 remains withdrawn as including a nonelected species. Applicants request search and rejoinder upon notice of allowable generic claim.

Interview Summary

Applicants thank Examiner Crowder and Examiner Gamble for the interview on October 18, 2006. We discussed the 112 rejections. Examiner Gamble indicates that nucleic acids are treated differently than proteins even if sequences are known. We discussed 102 rejections.

Restriction

The election of Group II (claims 55-101 and 103-114) with traverse, a species of antibody specific for VEGF, *E. coli* host cells, DsbA, the heavy and light chains encoded by a single polynucleotide and an IgG1 subtype is acknowledged. The finality of the restriction is acknowledged.

Restriction grouping II (claims 55-101 and 103-114) was previously elected. However, on the cover sheet PTO form 326 (Office Action Summary), the Office has incorrectly listed the claims under examination. Claims 1-54 and 102 (Restriction Grouping I), claims 115 and 117-120 (Restriction Grouping III) and claim 116 (Restriction Grouping IV) are withdrawn from examination as being directed to a non-elected invention. Additionally, claim 86 (directed to heavy and light chains encoded by separate polynucleotides) is withdrawn from examination due to species election requirement between single and separate polynucleotides. Otherwise, the remaining claims of the restriction grouping, *i.e.*, claims 87-101 are also under examination as claims 87-101 do not conflict with any species election requirement previously set forth. In addition, where a Markush grouping occurs in a claim (*i.e.*, claim 99), it is understood that while Applicants elected a species for examination on the merits (*i.e.*, DsbA in claim 99), that the Office will examine all species of the listing according to Markush practice.

In summary, claims 55, 57-85, 87-101 and 103-114 are under examination. Acknowledgement of the claims correctly under examination, or an explanation of why claims 87-101 are withdrawn from examination, is respectfully requested from the Office in the next Office communication. Claims 87-101 are free of any rejection made in the previous Office Action for at least the same reasons as claims 55, 57-85, and 103-114, below.

Priority Claim

Applicants note the claim for priority to U.S. provisional patent Application No. 60/422,952, filed Oct. 31, 2002, under 35 U.S.C. § 119(e) is acknowledged.

IDS Acknowledgement

Applicants note with appreciation the execution and return of the PTO 1449 forms filed 6/25/2004, 10/20/2004 and 05/02/2006.

Trademarks

Applicants believe the application correctly designates trademarked products where appropriate.

Objections to the Claims

Claims 63 and 64 are objected to because the claims allegedly recite informalities: DsbA and DsbC. The Office has suggested the claims be amended to recite the full name of "Dsb." Contrary to Office arguments, the term "Dsb" is not an "informality".

The term "Dsb" is an acronym for the phrase disulfide bond formation. See, Kurokawa (Kurokawa et al., JBC 276(17): 14393-14399 (2001)), at page 14393, left column, first full paragraph. Thus, "Dsb" is an art-recognized term. In addition, the Office is reminded that Applicants are permitted to be their own lexicographer. Use of the art-recognized term "Dsb" is permitted. Applicants are not required to provide "a full name" or definition of the acronym.

In view of the above, the meaning of "Dsb" in both claims 63, 64, and elsewhere, is believed to be clear. Reconsideration and withdrawal of the objections is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 55, 58-85 and 103-114 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter regarded as the invention. The rejection is respectfully traversed.

a) Claims 55 and 58-65 are allegedly indefinite because they depend on non-elected claims. In response, claims 55 and 58-65 have been amended, and, no longer depend from non-elected claims.

b) Claims 66-85 and 103-114 are allegedly indefinite in the recitation of "The method" in the preamble without setting forth and distinctly claiming the subject matter of the claimed invention. While not acquiescing to the rejection and solely to expedite prosecution, claim 66 now refers to "A method for producing an antibody..." The amendments to claim 66 are believed to overcome the rejection. The rejection of dependent claims 67-85 and 103-114 is overcome by virtue of dependency from claim 66.

c) Claim 113 is allegedly indefinite in the recitation of "the amount of claim 112." Claim 113 is amended, and as such, is believed to be free of the rejection.

In view of the amendments to the claims, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 55-85 and 103-114 are rejected under 35 U.S.C. § 112, first paragraph, in that they allegedly fail to comply with the written description requirement. The rejection is respectfully traversed. Claim 56 has been cancelled rendering the rejection of this claim moot.

In summary, the Office argues (Office arguments, Office Action at 5-7) the specification fails to describe any "polynucleotide encoding the antibody or immunoconjugate" and that the specification, as filed, does not disclose a sufficient number of species to support the "polynucleotide" as broadly encompassed by the claimed invention. The Office argues the claimed polynucleotide would encompass genes or continuous or discontinuous regions of nucleic acids encoding an antibody as well as encompassing the genomic sequence (*i.e.*, the V, D, J regions and the heavy and light chain variable and constant regions) encoding an antibody. The Office further

argues that Applicants were not in possession of the structural attributes of a representative number of species possessed by a member of the genus of a "polynucleotide encoding the antibody."

As noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶1, "Written Description" Requirement ("the guidelines"), there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed, 66(4) *Fed Reg.* 1099, 1105 (2001); *see also, In re Wertheim,* 191 USPQ 90,97 (CCPA 1976). The guidelines further state that "[(The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) *Fed. Reg.* at 1107; 191 USPQ at 97, (emphasis added). Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow,* 217 USPQ 1089 (Fed. Cir. 1991).

Independent claim 55 now refers to an isolated polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a hinge region which does not form inter-heavy chain disulfide linkages. Claim 66 now refers to a method of producing an intact antibody comprising expressing in a prokaryotic host cell the polynucleotide of claim 55, wherein the amount of intact antibody produced from the host cell is increased in comparison to the amount of aggregated heavy chain produced in the host cell, and recovering said intact antibody from the host cell. Claim 105 now refers to a method for producing an intact antibody comprising: expressing in a prokaryotic host cell a polynucleotide encoding a variant immunoglobulin heavy chain; wherein said variant immunoglobulin heavy chain comprises a reduced ability to form a disulfide linkage such that amount of self aggregation of the variant immunoglobulin

heavy chain is less than the amount of self aggregation of a reference immunoglobulin heavy chain when expressed under similar conditions, wherein the reference immunoglobulin heavy chain has a wild type ability to form a disulfide linkage.

In the Office action, the Examiner seems to take the position that written description requires precise sequence information and actual reduction to practice of every embodiment. However, the Federal Circuit has maintained that precise sequence information and actual reduction to practice of every embodiment is not necessary to meet the written description requirement.

> "The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed" 418 F.3d 1349, 1357 (Fed. Cir. 2005) The Board was correct, however, not to view as dispositive that Inglis had not actually produced a poxvirus vaccine, [n10] because an actual reduction to practice is required for written description.
> *Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006).

Moreover, the Federal Circuit also stated that recitation of known structure is not required to satisfy written description. The court indicated where accessible literature sources provide sequences, satisfaction of written description does not require recitation of sequences in the specification. Falkner v. Inglis, 448 F.3d 1357, 1363 (Fed. Cir. 2006).

The specification provides a number of examples of representative species of "the genus." The antibodies having the variant heavy chain hinge region, specifically bind to a wide variety of antigens, including but not limited to, polypeptides, (*see,* U.S. published patent application no. 2005/0048572 A1, the publication number of the instant application) ([0107]); cell receptors ([0108]); tumor antigens ([0109]); cell survival regulatory factors ([0110]), and others as disclosed throughout the specification. Paragraphs [0080], [0101], and [0102] describe the types of altered or variant heavy chains having no ability, or reduced ability, to form disulfide linkages. The specification is replete with examples of heavy chain variant regions having one or more cysteine

residues replaced with serine residues. *See*, for example, Plasmid paTF320 [0247], having both hinge cysteines converted to serine; Plasmid paTF262 [0241], having the first hinge cysteine converted to serine; and, Plasmid pVG126 [0238] having a second hinge cysteine converted to serine. The polypeptide and nucleic acid sequences of paTF50, pxTFZAPZZ, pxVG2AP11, pxVG11VNERK, and pxTF7T3H are described(see Figures 1-4 and 7).

The art is replete with a large number of antibodies which have been cloned and the nucleotide sequences encoding both the heavy and light chains obtained. *See*, for example, [0065]-[0069], describing antibodies, the types of antibodies known in the art, and, the functional parts of antibodies. The cDNA sequences of many antibodies, antibody parts (*i.e.*, heavy chain, light chain, CDR regions, Fc regions, constant regions, variable regions, etc.), as well as the genomic nucleotide sequences, are publicly available. The claimed invention is not dependent upon the specificity of the antigen binding region (*i.e.*, anti-VEGF antibodies) as the claimed invention is concerned with, *inter alia*, prokaryotic expression and production of antibodies comprising modified hinge cysteine residues (Abstract). See, for example, original claim 80, claiming IgG, IgA and IgD antibodies. Just as a polynucleotide sequence comprising a cDNA can be expressed in a wide variety of host cells, or expressed from a wide variety of expression vectors, a heavy chain having a variant heavy chain hinge region can be a part of any number of antibodies, regardless of the antigen binding specificity of the variable regions. Moreover, one of skill in the art can readily modify nucleic acids disclosed in the specification to encode other antibodies. Sequences of antibodies and antibody hinge regions can be readily determined by those of skill in the art.

If the Office maintains this rejection, the Office is respectfully requested to provide more specific comments regarding the specific reasons the claims allegedly fail meet the written description requirement of 35 U.S.C. § 112, first paragraph.

In view of the amendments to the claims and arguments above, the rejection under 35 U.S.C. § 112, first paragraph, is believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(b)

Claims 55-59, 65-86, and 104 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gillies et al. (Human Antibody Hybridomas 1:47-54 (1990)) ["Gillies"] and Davis et al. (EMBO Journal 8: 2519-2526 (1989)) ["Davis"]. The rejections are respectfully traversed. Claim 56 has been cancelled rendering the rejection of this claim moot.

Gillies is cited by the Office for allegedly teaching methods of constructing vectors encoding chimeric antibodies having 1) deletion of the entire CH2 domain, and 2) mutation of two hinge cysteine residues to serine residues. Gillies is also cited for allegedly teaching methods of making the mutant antibody using host cells and that the mutant antibody has normal antigen binding activity but greatly reduced ADCC and CDC.

Davis is cited by the Office for allegedly teaching methods of making IgM by replacing cysteine residues responsible for formation of inter-heavy chain disulfide bonds at positions 337, 414, and 575 with serine. Davis is also cited for allegedly teaching methods of making the IgM variant using recombinant plasmid vector containing the polynucleotide encoding the antibody variant and host cells.

Contrary to the opinion of the Office, neither of Gillies or Davis anticipates claims 55, 57-59, 65-84, 86, and 104. In the instant case, the Office has failed to specifically point out where Gillies or Davis teaches a polynucleotide molecule encoding an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a heavy chain hinge region which does not form inter-heavy chain disulfide linkages, as is currently claimed in claims 55, 57-59, 65-84, 86 and 104. Gillies et al. describes a heavy chain with cysteines replaced with serine that formed an antibody HL fragment and not an H_2L_2. Figure 5A of Gilles et al. on page 51 does not show migration on an unreduced gel of an H_2L_2 antibody, but rather a HL fragment. See page 51 of Gillies et al. In addition, in contrast to the present invention, Gillies et al showed substantial heavy chain dimer formation. Whereas, Applicants surprisingly found that

intact antibodies were formed and the amount of heavy chain aggregation was decreased when the formation of inter-chain disulfide linkages was reduced.

Davis et al. describes mutations at Cys residues at position 337 (CH2), 414 (CH3), and 575 (tail) of IgM molecule involved in forming pentamers or hexamers of the IgM molecule and does not describe a heavy chain variant comprising a heavy chain hinge region that does not form interheavy chain disulfide linkages. The cysteine residues of Davis et al, are not found in the hinge region but rather are found in other domains of the Fc portion of the antibody.

As the Office is aware, in order for a reference to anticipate, the reference must teach each and every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Because Gillies or Davis fails to teach each and every element of the claims, they do not anticipate the claimed subject matter.

In view of the amendments to the claims and arguments above, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 102(e)

Claims 55-85 and 103-114 are rejected under 35 U.S.C. § 102(e) as being anticipated by Simmons et al. (U.S. patent appl. no. 2005/0170464) ["Simmons"]. The rejection is respectfully traversed. Claim 56 is cancelled rendering the rejection of this claim moot.

The Office argues that given the amino acid sequences of the Fc regions including the hinge regions were well known in the art, one of skill would immediately envisage that Simmons taught the amino acid substitution from cysteine to serine in the Fc region including those cysteine residues in the hinge region that are responsible for forming inter-heavy chain disulfide bonds.

However, whether one of skill would "immediately envisage" that Simmons teaches the amino acid substitution from cysteine to serine residues in the Fc region is not

the correct legal standard for anticipation. As the Office is aware, and as discussed above, in order for a reference to anticipate, the reference must teach each and every element of the claims. Simmons discloses substitution of any cysteines not involved in maintaining proper conformation of the antibody. See paragraph 0132 of Simmons. There is no teaching and suggestion in Simmons that every cysteine can therefore be substituted. Simmons fails to disclose a heavy chain that comprises a variant heavy chain hinge region. Surprisingly, Applicants found that when the formation of inter-chain disulfide linkages was reduced intact antibodies could still be formed and the amount of heavy chain aggregation was decreased.

Thus, because Simmons does not teach each and every element of the claims, Simmons cannot, and does not, anticipate claims 55, 57-84, and 103-114. In view of the amendments to the claims and arguments above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 55-85 and 103-114 are rejected under 35 U.S.C. § 103(a) as being anticipated by Gillies et al. (Human Antibody Hybridomas 1:47-54 (1990)) ["Gillies"] and Davis et al. (EMBO Journal 8: 2519-2526 (1989)) ["Davis"] in view of Georgiou et al. (U.S.P.N. 5,264,365) [Georgiou] and Kurokawa et al. (JBC 276:14393-14399 (2001)) [Kurokawa]. The rejection is respectfully traversed. Claim 56 is cancelled rendering the rejection of this claim moot.

The Office incorporates the arguments concerning Gillies and Davis as set forth above (Office Action at 10-12). The Office further argues the reference teachings differ from the claimed invention by not describing *E. coli* host cells with DsbA and deficient in endogenous protease activities. The Office argues that it would have been obvious to the ordinary artisan at the time the invention was made to make an antibody comprising a variant heavy chain hinge region that does not form an inter-heavy chain disulfide linkage using *E. coli* with Dsb proteins and deficient in proteases.

However, contrary to Office arguments, claims 55, 57-84, and 103-114 are not rendered obvious by any of Gillies, Davis, Georgiou and Kurokawa, alone or in combination. Even if combined these references do not disclose all of the elements of the claims. Applicants' arguments concerning the teachings of Gillies and Davis, above, are incorporated herein. Briefly, neither Gillies or Davis teach a polynucleotide encoding an intact antibody comprising a variant heavy chain, wherein the heavy chain variant comprises a hinge region that does not form inter-heavy chain disulfide bonds. Kurokawa is directed to NGF and enhancing formation of disulfide bonds rather than a situation where such bonds are not formed. Georgiou is directed to forming E. coli strains deficient in proteases. There is no teaching or suggestion in the references even when combined of a polynucleotide encoding an intact antibody comprising a variant heavy chain as claimed.

As the Office is aware, there are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obviousness was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Moreover, there is no motivation to combine these references. Davis is concerned with understanding the linkage of antibodies to form an IgM subunit and does not discuss hinge region inter-heavy chain disulfide bonds or production of antibodies in cells. Gillies is concerned with the interaction of the effector function and antigen binding

function of antibodies and not with increasing intact antibody production in cells. Kurokawa is directed to enhancing disulfide bond formation. Georgiou is directed to E. coli cells deficient in proteases. Thus one of skill in the art would not motivated to combine these references to achieve the claimed methods or polynucleotides.

In view of the amendments to the claims, and arguments above, the rejection under 35 U.S.C. § 103(a) is believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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